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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,954	08/03/2001	Mikio Takaiwa	211381US0CONT	9468

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 08/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,954	TAKAIWA ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *4-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/509,814* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-6 are still at issue and are present for examination. Claims 1-3 are now under consideration. Claims 4-6 remain withdrawn from consideration as being drawn to non-elected invention.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-3 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that Examiner has not provided adequate reasons and/or examples to support a conclusion of patentable distinctness between the identified groups. Applicants argue that the Examiner has not provided any explanation as to how the polypeptide of group I can be used to catalyze a hydrolytic reaction, nor has he provided any examples to support the same. Applicants therefore allege that Office has made an unsupported conclusion. Examiner respectfully disagrees with such an argument. Applicants claim in claim 1-3 a polypeptide with a protease activity, i.e., an enzyme which hydrolyzes proteins or digests proteins or degrades proteins. Such knowledge is common in the art and there is no need for the Examiner to provide examples for the same. Furthermore, group II is drawn to polynucleotides which are also called nucleic acids, polymers of four different nucleotides which are structurally and functionally different from a polypeptide which are polymers of 20 different amino acids. This basic information is common knowledge in the art. Contrary to applicants argument the inventions are distinct as explained in the previous Office action and therefor the restriction is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claims 4-6 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 9.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/509,814, filed on 4-6-2000. ***Drawings***

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. While Examiner notes that applicants have indicated SEQ ID NOs for sequences in figures 7 and 8, it is not clear as to which SEQ ID NO corresponds to which sequence. See particularly 37 CFR 1.821(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 is drawn to an alkaline protease of claim 1 or 2 which has an amino acid sequence SEQ ID NO:2 **or** such a sequence in which one or more amino acids are deleted, substituted or added. The recitation of the phrase "such a sequence in which one or more

amino acids are deleted, substituted or added" does not further limit the claim from claims 1 or 2 thus rendering claim 3, indefinite. Examiner suggests applicants to recite claim 3 independent of claims 1 and 2 or amend the claim in its entirety such that it is further limiting.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an alkaline protease enzyme having the physicochemical properties as described in claims 1 and 2 along with amino acid sequence as set forth in SEQ ID NO:2, does not reasonably provide enablement for any or all such enzymes from any or all sources, comprising similar physicochemical properties and a modified amino acid sequence in which one or more amino acids are deleted, substituted or added to SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-3 are so broad as to encompass any protease having any amino acid sequence and the physicochemical characteristics of claims 1 or 2. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of such proteases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single protease. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides with said function/activity. The specification is limited to teaching the use of SEQ ID NO: 2 as a protease but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any protease because the specification does not establish: (A) regions of the protein structure which may be modified without affecting protease activity; (B) the general tolerance of said proteases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in the protease with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including proteases with an enormous number of amino acid modifications of SEQ ID NOS:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of proteases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 6,376,227 B1. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-2 of the instant application and claims 1 and 3 of the reference patent are both directed to protease having an amino acid sequence SEQ ID NO:2 and claim 3 of the instant application is directed to a variant of the same comprising an alteration at an amino acid corresponding to one or more positions in SEQ ID NO:2. Among all the variant polypeptides claimed in the instant application and the polypeptide claimed in the reference patent a good number are identical to one another. The portion of the specification (and the

claims) in the reference patent that supports the recited amino acid SEQ ID NO:2 includes several embodiments (amino acid positions) that would anticipate the positions claimed in claims 1-3 herein. Claims of the instant application listed above cannot be considered patentably distinct over claims 1 and 3 of the reference patent when there is specifically recited embodiment that would anticipate mainly claims 1-2 and 3 of the instant application. Alternatively, claims 1-3 cannot be considered patentably distinct over claims 1 and 3 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 1 and 3 of that patent and falls within the scope of claims 1-3 herein because it would have been obvious to one having ordinary skill in the art to modify claims 1 and 3 of the reference by selecting a specifically disclosed embodiment that supports those claims i.e., a variant of SEQ ID NO:2. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claims 1 and 3 of the reference patent.

Conclusion

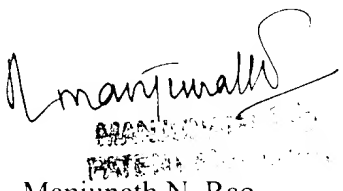
None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



Manjunath N. Rao
August 21, 2003